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MEMORANDUM

SUBJECT: ***ENDOSULFAN*** - Report of the FQPA Safety Factor Committee.

FROM: Brenda Tarplee, Executive Secretary
FQPA Safety Factor Committee
Health Effects Division (7509C)

THROUGH: Ed Zager, Chair
FQPA Safety Factor Committee
Health Effects Division (7509C)

TO: Steve DeVito, Risk Assessor
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Health Effects Division (7509C)

PC Code: 079401

The Health Effects Division (HED) FQPA Safety Factor Committee met on November 2, 1998 to evaluate the hazard and exposure data for endosulfan and recommended that the FQPA Safety Factor (as required by Food Quality Protection Act of August 3, 1996) be reduced (to 3x) in assessing the risk posed by this chemical.

I. HAZARD ASSESSMENT

1. Determination of Susceptibility

The Hazard Identification Assessment Review Committee (HIARC) determined that the available Agency Guideline studies indicated no increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to Endosulfan. In the prenatal developmental toxicity studies in rats and rabbits, developmental toxicity was seen only in the presence of maternal toxicity. In the two-generation reproduction study in rats, effects in the offspring were observed only at or above treatment levels which resulted in evidence of parental toxicity (*Memorandum:* D. Liem and J. Rowland to S. DeVito dated October 7, 1998).

2. Open Literature Data

Lakshmana and Raju (1994) administered endosulfan via gastric intubation to Wistar rat pups of both sexes at 6 mg/kg body weight/day from post-natal days 2-25. Its effect on levels of noradrenaline (NA), dopamine (DA) and serotonin (5-HT) was assayed in olfactory bulb (OB), hippocampus (HI), visual cortex (VC), brainstem (BS) and cerebellum (CB) on days 10 and 25 using high-performance liquid chromatography (HPLC). The activity of acetylcholinesterase (AChE) was also estimated in the same regions of the brain. Performance in operant conditioning for solid food reward was assessed in 25-day-old rats. NA levels were increased in OB (12%, P = 0.01) and BS (10%, P = 0.05) at 10 days of age and in HI (20%, P = 0.01) and CB (12%, P = 0.05) at 25 days of age. DA levels were decreased in HI at both 10 (42%, P = 0.001) and 25 (45%, P= 0.001) days. Serotonin levels were increased in OB (12%, P = 0.05), HI (41%, P = 0.001), VC (30%, P= 0.01) and BS (15%, P= 0.01) at 10 days of age but at 25 days, levels were decreased in BS (20%, P = 0.05) and CB (31%, P = 0.01). The activity of AchE was not different from the control groups in any of the regions studied. The investigators suggested that monoaminergic systems in the developing rat brain respond to endosulfan by undergoing something like a 'reorganization'. However, such changes do not ameliorate certain functional losses following the exposure to endosulfan as operant conditioning revealed deficits in acquisition as well as retention of memory (Reference: Lakshmana, M.K. and Raju, T.R., 1994. Endosulfan induces small but significant changes in the levels of noradrenaline, dopamine and serotonin in the developing rat brain and deficits in the operant learning performance. *Toxicology;*91: 2, 1994:139-50).

3. Adequacy of Toxicity Database

The HIARC determined that the requirement for a developmental neurotoxicity study in rats was reserved for endosulfan pending the receipt and review of a subchronic neurotoxicity studies in rats. However, **the FQPA Safety Factor Committee concluded that a developmental neurotoxicity study in rats is required for endosulfan** due to concern by the Committee for: 1) the fetal effects reported in the open literature abstract (discussed above); 2) the severity of effects seen in the female offspring of the F_0

generation (increased pituitary) and F_1b generation (increased uterine weights) at the high-dose when compared to the toxicity observed in parental animals (decreased body weight) at this dose in the two-generation reproduction study in rats; and 3) the subchronic neurotoxicity study (requested by the HIARC) will only address the neuropathological concerns resulting from exposure to endosulfan - a developmental neurotoxicity study will provide the critical data demonstrating the toxic effects of endosulfan on the developing fetal nervous system.

NOTE: The Agency should be consulted with respect to the Developmental Neurotoxicity study design / protocol.

II. EXPOSURE ASSESSMENT AND RISK CHARACTERIZATION

1. Dietary (Food) Exposure Considerations

Endosulfan is widely used on many agricultural crops and also in residential settings as an insecticide and aracicide. The chemical is a mixture of isomers and the tolerance expression includes the alpha, beta isomers plus a sulfate metabolite.

Tolerances for residues of Endosulfan and its metabolites are established in/on many RACs including fruits, vegetables grains, milk and meat at levels ranging from 0.1 ppm to 2.0 ppm (40CFR180.182). Codex maximum residue limits (MRLs) for residues of Endosulfan are established in/on various plant and animal commodities.

There are numerous field trial data on various commodities, reflecting various application sites throughout the country. Additionally, PDP and FDA monitoring data are available for endosulfan. Residues of endosulfan have been reported by PDP and FDA in a variety of crops. For example, in 1995 endosulfan was detected in apples (7%), carrots (4%), grapes (4%), green beans (24%), peaches (8%), potatoes (20%), spinach (14%), corn (0.1%), peas (0.3%), and oranges (2%) - for which there is no tolerance. The Limit of Quantitation (LOQ) for these data is ~0.01 ppm.

The HED Dietary Exposure Evaluation Model (DEEM) is used to assess the risk from acute and chronic dietary exposure to residues of Endosulfan in food. These analyses are based on the consumption database used by DEEM using reassessed tolerance values.

2. Dietary (Drinking Water) Exposure Considerations

A drinking water exposure assessment for Endosulfan had not yet been performed at the time of this meeting. EFED is in the process of: 1) completing the environmental fate assessment (as quantitative an evaluation as possible); 2) modeling exposures for high use crops and other potentially vulnerable sites (which will be determined after the Smart meeting with the registrant); and 3) evaluating the extent and quality of existing monitoring data, if necessary.

The environmental fate data base for Endosulfan is not complete. EFED is currently in the process of reviewing new studies submitted by the registrant to fulfill Agency data requirements and investigating other sources of data for endosulfan. Once data review is completed, a quantitative fate assessment sufficient for assessing drinking water exposure can be developed.

Supplemental studies listed in the EFGWB One-Liner Database suggest that endosulfan may be moderately persistent in soils but its high affinity to sorb to soil particles, reduces its susceptibility to leaching. Although endosulfan does not appear to be highly mobile, it may be persistent enough in some instances to move to ground water (detects have been reported in the EPA Pesticides in Ground Water Database). Movement to surface water sources of drinking water is likely to occur via spray drift and runoff adsorbed to soil particles. This is supported by several studies which have reported endosulfan detects in surface water.

Endosulfan consists of isomers which appear to have some differences in persistence. The extent to which these differences will affect the fate assessment, if any, is not yet known. Endosulfan sulfate is expected to be the degradate of concern. Further information on the fate of this degradate is under investigation.

Ground water and surface water EECs for Endosulfan will be based upon modeling and supported by any available monitoring data. The EFED models used for ground and surface source drinking water exposure assessments result in estimates that are considered to be upper-bound concentrations.

3. Residential Exposure Considerations

Residential uses of the insecticide, endosulfan, include applications made to ornamentals and small fruit trees and to home vegetable gardens. It is formulated as a liquid spray (maximum rate of one pound per acre) and as a dust (maximum rate of 3.5 pounds per acre). The frequency of application varies with each crop ranging from 1-5 applications per growing season. Exposure to infants and children could occur during and after application of Endosulfan. For example, toddlers could be exposed from incidental soil ingestion by hand-to-mouth activity in garden plots.

Chemical-specific product use information for endosulfan was provided via the LUIS report from BEAD. A large sample of labels are also being used to ascertain the use pattern, potential exposure scenarios, and exposed populations of concern.

There are currently no chemical- or site-specific data available to assess the exposure resulting from the residential use of endosulfan. The Pesticide Handler Exposure Database (PHED) and/or the Draft HED Standard Operating Procedures (SOP) for Residential Exposure Assessments will be used for all residential calculations with no

deviations made to the SOP assumptions. A dermal absorption factor of 45% will be used with the oral dose and endpoint selected for intermediate and chronic risk assessments. This value (45%) is based on data from two dermal absorption studies in rats (§85-2; MRID Nos. 40223601 and 41048504).

III. SAFETY FACTOR RECOMMENDATION AND RATIONALE

1. FQPA Safety Factor Recommendation

The Committee recommended that the **FQPA safety factor** for protection of infants and children (as required by FQPA) be **reduced to 3x.**

2. Rationale for Reducing the FQPA Safety Factor

The HIARC determined that there is: 1) no indication of increased susceptibility of rats or rabbit fetuses to *in utero* exposure in the developmental toxicity study for endosulfan; 2) quantitatively, no indication of increased susceptibility to rat offspring following pre- and/or post-natal exposure in reproductive study; and 3) no evidence of adverse effects on the developing fetal nervous system in any of these studies. Therefore, the HIARC, using a tiered approach, placed the requirement for a developmental neurotoxicity study in reserve pending the receipt of the subchronic neurotoxicity study.

However, the FQPA Safety Factor Committee concluded that it was appropriate to request the developmental neurotoxicity study in rats at this time because the subchronic neurotoxicity study will only address the neuropathological concerns in adults and not the concern for effects in developing fetuses. The developmental neurotoxicity study is requested at this time because of the concern for: 1) the fetal effects reported in the open literature abstract (Lakshmana et al., 1994); and 2) the severity of effects seen in the female offspring of the F_0 generation (increased pituitary) and F_1b generation (increased uterine weights) at the high-dose when compared to the toxicity observed in parental animals (decreased body weight) at this dose in the two-generation reproduction study in rats.

The FQPA Safety Factor Committee concluded that the **FQPA safety factor** is required, however can be **reduced to 3x** because: 1) there is no evidence of increased susceptibility in any study; 2) the severity of the fetal effects in the reproduction study were not consistent between generations and the target organ toxicity seen in this study was not seen in any other study; and 3) reliable data and conservative assumptions in screening level models were used to assess the potential dietary (food and water) and residential exposure to this chemical. Consequently the FQPA safety factor was reduced based on the uncertainty associated with the data gap for a developmental neurotoxicity study in rats.

3. Population Subgroups for Application of the Safety Factor

The Committee determined that the FQPA safety factor (3x) is applicable for the following subpopulations:

Acute Dietary Assessment: All populations which include Infants and Children. The FQPA factor is appropriate for these populations due to the uncertainty regarding the effects on the developing fetal nervous system (data gap). This uncertainty is being addressed by the requirement of a developmental neurotoxicity study in rats.

Chronic Dietary Assessment: All populations which include Infants and Children. The FQPA factor is appropriate for these populations due to the uncertainty regarding the effects on the developing fetal nervous system (data gap). This uncertainty is being addressed by the requirement of a developmental neurotoxicity study in rats.

Residential (Short-, Intermediate- and/or Long-Term) Assessment(s): All populations which include Infants and Children. The FQPA factor is appropriate for these populations since the potential for residential exposure to infants and children resulting from the use of endosulfan exists and there is uncertainty regarding the effects on the developing fetal nervous system after such exposure. This uncertainty is being addressed by the requirement of a developmental neurotoxicity study in rats.